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STUDIES IN INFLUENZA AND PNEUMONIA

STUDY VIII. EXPERIMENTS ON THE ETIOLOGY OF "GASTRO-INTESTINAL" INFLUENZA

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Symptoms of gastro-enteritis, alone or in association with respiratory involvement, have occurred with such regularity during the course of epidemics of influenza and the accompanying prostration has been so pronounced, that a gastro-intestinal type of this disease has come to be quite generally recognized. Kuskow cites cases of his own and of others in which lesions of the gastro-intestinal tract were found, varying from simple enteritis with the swelling of Peyer's patches and hyperplasia of mesenteric lymph glands to severe ulcerative and hemorrhagic gastro-enteritis. Bacteriologic studies, however, are quite lacking; no one has demonstrated bacteria in the lesions, and many regard the severe cases as due to enteritidis-like organisms. The investigations of Sherwood, Downs, and McNaught do not support the latter view since this type of organism was isolated in cases of influenza without symptoms referable to the gastro-intestinal tract and in those with symptoms. I shall report herewith the results of a study of a series of cases of gastro-enteritis, including one fatal case, which occurred during the first two waves of the epidemic of 1918.

The incidence of gastro-enteritis during the first wave was quite high; it was more common in children, but occurred also in adults. The symptoms varied greatly, but prostration and high fever were the striking features. In some instances the symptoms referable to the gastro-intestinal tract occurred without accompanying respiratory involvement; in most instances more than one member of a given family were affected. Cultures from the stools, usually from only one specimen taken at the height of the attack, were made in 15 cases during the first wave. Flakes of bloody mucus were fished out and washed in salt solution and plating on blood-agar made. Varying numbers of green-producing streptococci resembling those from the sputum in influenza were isolated in 9 instances and hemolytic streptococci were isolated in 2. Influenza bacilli were not isolated. Smears from flakes of bloody mucus often showed a large number of gram-positive diplococci resembling those from the sputum. Owing to stress of other work no animal experiments were made at this time. During the second wave opportunity presented itself for the study of one fatal case and one other case in the same family. The findings in detail are:

Case 2979,—A boy aged 3, a patient of Dr. C. T. Granger, after having had symptoms of a slight sore throat for several days, suddenly became ill Feb. 3, 1919, with vomiting, diarrhea, high fever and delirium. The stools showed blood on the first day; this continued and he passed almost pure blood and mucus at times. He grew gradually weaker, vomited blood February 9 and died the following day. Dr. Peters brought the internal viscera to me for examination. The lungs revealed marked hypostatic congestion, moderate edema, but no outspoken areas of consolidation. The stomach contained a moderate amount of dark red, partially clotted, blood. The mucous membrane was covered with chocolate colored blood mixed with mucus. This was removed and numerous small hemorrhages with beginning ulceration, more numerous in the pyloric end, were found. The duodenum was normal. The mucous membrane of the ileum was extensively hyperemic throughout and was covered with mucopurulent bloody material; numerous punctate hemorrhages and in places beginning ulceration were found. The mesenteric lymph glands were edematous and hemorrhagic. The kidneys showed marked cloudy swelling; the spleen and heart were normal. Blood-agar plate cultures of an emulsion of the hemorrhagic mucous membrane of the stomach contained fully 5,000 rather moist, green colonies of bacteria resembling pneumococci and 5 colonies of staphylococci. The emulsion of the mesenteric lymph glands contained 260 colonies of green-producing streptococci, 4 of staphylococci, and a number of colonies of Bacillus coli. Emulsions of the washed intestinal wall revealed 120 colonies of green-producing streptococci, 50 colonies of staphylococci, and 30 colonies of Bacillus coli. Cultures of the spleen were negative. In sections made through the hemorrhagic areas in the ileum were found wedge shaped and diffuse areas of hemorrhage in the mucosa, with only moderate infiltration and edema, and in some instances with superficial ulceration of the mucosa (fig. 1). A large number of gram-positive diplococci were found throughout the hemorrhagic areas, but were most numerous near or on the surface of the ulcerated area (fig. 2a). The hemorrhagic areas in the stomach showed a similar picture; they contained a large number of gram-positive diplococci. In either case few or no diplococci were demonstrable in the tissues without lesions.

Feb. 12, 1919, the primary culture in dextrose-brain broth of the emulsion of a mesenteric lymph gland was injected, under ether, through a laparotomy incision into the duodenum of one guinea-pig. The leukocyte count was 25,000 before injection. The animal was found dead the following day. Examination revealed 7,200 leukocytes, fibrinous and clotted blood deposit about the point of puncture of the duodenum, a normal intestine above this point, and an extremely hyperemic intestine below. The lumen of the intestine contained a large amount of mucus mixed with chocolate colored blood. The mesenteric lymph glands were edematous. The mucous membrane of the stomach, the uterus, and the cecum was hyperemic and contained a few hemorrhages. The primary culture in glucose-brain broth of the stomach emulsion of the patient was injected in doses varying from 0.1 to 1.5 c c, intratracheally into one monkey and 5 guinea-pigs, and intravenously into one rabbit. The guinea-pig that was given 0.5 c c and the one given 1 c c died in twenty-four hours. Both had hemorrhagic edema of the lungs and hemorrhagic pleuritis; one had marked lesions of the intestine and stomach, the other slight lesions. The other 3 animals were chloroformed for examination the third day. All had bronchopneumonia, one had a large amount of turbid fluid in the pleural cavity, and 2 had lesions of the intestinal tract; cultures from the lung of one of these were agglutinated specifically by the monovalent antistreptococcus serum. One of the guinea-pigs had leukopenia, 1 leukocytosis, and in 2 there was no change in the leukocyte count. The monkey died in twenty-four hours. Examination revealed hemorrhagic edema of the intermediate lobe, marked distention of the stomach with gas rich in carbon dioxid, edematous and hemorrhagic Peyer's patches and mesenteric lymph glands, and hyperemia and edema of the mucous membrane of the small intestine, especially in the ileum, where it was covered with mucus containing flakes of blood. The leukocyte count dropped from 35,000 before injection to 7,200 after death. The blood

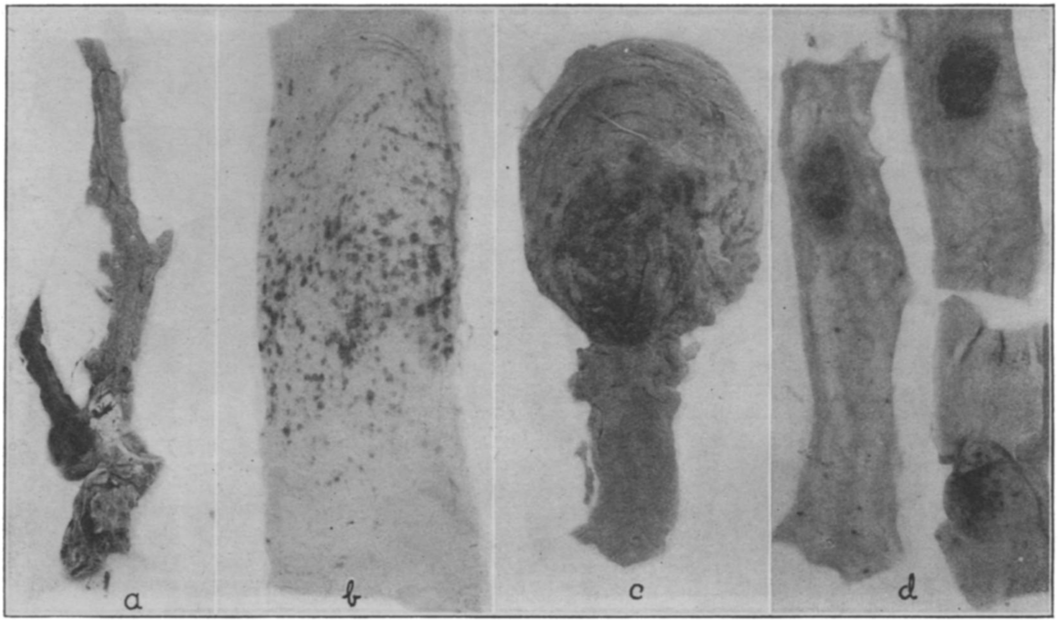

Fig. 1.—Photographs of lesions of the pancreas, intestine, stomach, and Peyer's patches following injection of green-producing streptococcus from influenza. × I.

a. Pancreas of guinea-pig forty-eight hours after intravenous injection of a strain after one animal passage. Note the edema, hemorrhage, and fat necrosis; × I.

b. Ilium of rabbit twenty-four hours after intravenous injection of a strain in the third animal passage. Note the numerous circumscribed hemorrhages in the mucous membrane; × I.

c. Edema and extensive hemorhages in the stomach of a guinea-pig fifteen days after intratracheal injection of a strain in the third subculture; × 0.5.

d. Swelling and hemorrhages of Peyer's patches and the mucous membrane of the duodenum in the ileum and duodenum of rabbit forty-eight hours after intravenous injection of a strain in the fourth animal passage.

contained a moderate number of green-producing streptococci and staphylococci; the upper intestinal contents, a moderate number of staphylococci and green-producing streptococci; the lower intestinal contents, colon bacilli only. Cultures from two mesenteric lymph glands, the kidney, and the peritoneum were negative. Sections of the lower ileum contained subperitoneal hemorrhages and areas of hemorrhage in the mucous membrane showing desquamation of epithelium but no distinct ulceration. A large number of gram-positive diplococci were found in the hemorrhagic areas of the mucous membrane (fig. 3), a smaller number in the subserous hemorrhages, but none in the adjoining normal tissue. The rabbit injected intravenously with the primary culture from the stomach emulsion developed diarrhea and died three days later. Examination revealed two areas of bronchopneumonia posteriorly in the diaphragmatic lobes, hyperemia of the small intestine, swollen Peyer's patches and lymph follicles, much mucus in the intestine, edematous mesenteric glands, embolic lesions in the medulla of the kidney, and a few lesions in the myocardium and skeletal muscles. Cultures from the blood were negative and those from the pneumonic areas in the lung contained green-producing streptococci and staphylococci.

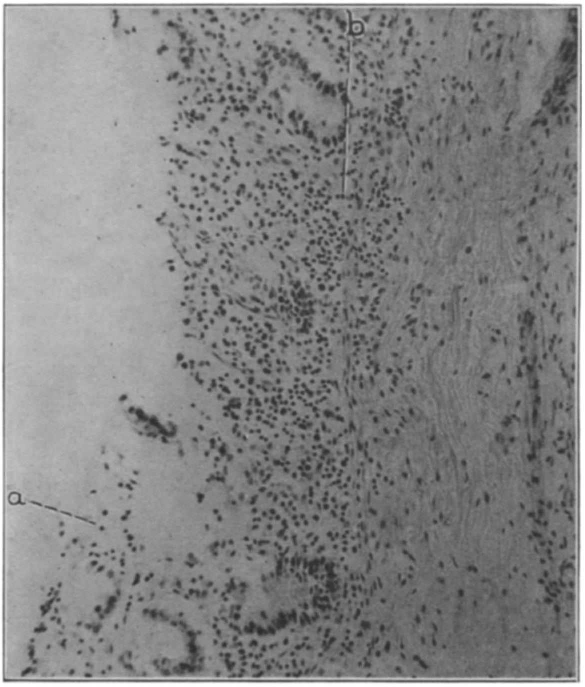

Fig. 2.—Photomicrograph of section of ileum in case 2979. Note the loss of tissue, infiltration by erythrocytes and leukocytes; hematoxylin and eosin, × 100.

Case 2981.—A baby girl aged fifteen months, sister of the patient whose case (case 2979) is first recorded, became ill Jan. 9, 1919, with vomiting, high fever (104 F.), and diarrhea six days after her brother had been taken sick. January 11, the child was apathetic, and fussy; the fever and diarrhea continued, and the leukocyte count was 5,400. The skin was dry and without rash, and there was no throat infection; the abdomen was scaphoid; and the stool consisted largely of blood-tinged mucus resembling pus. The diarrhea continued for five days, after which the child gradually recovered. Cultures were made from the tonsils, and from four samples of bloody mucus in the stool. The cultures from the tonsils showed the usual streptococcal flora. The blood-agar plates of the bloody mucus contained countless numbers of Bacillus coli, a few staphylococci, and rather moist, green-producing colonies of streptococci. Three guinea-pigs were injected, one intrarectally, one intratracheally with a salt solution suspension of the bloody mucus, and one with the pure culture of green-producing streptococcus in the second generation. The guinea-pig injected intrarectally appeared well the following day when it was chloroformed. In the cecum were a large number of small hemorrhages and swollen lymphoid follicles; in the stomach, large circumscribed areas containing small punctate hemorrhages surrounding the cardiac orifice; and in the duodenum a few hemorrhages in the mucous membrane just beyond the pyloric ring. Cultures from the blood, adrenal, spleen, kidney, and liver were negative; staphylococci and green-producing streptococci were produced from the mesenteric and perigastric lymph glands, and from the lung. Sections of the hemorrhagic areas in the duodenum showed marked extravasations of red blood corpuscles, especially in the submucosa in which a large number of diplococci were found. In the guinea-pig injected intratracheally with a suspension the leukocyte count dropped 66 per cent. the following day. The temperature increased 2 degrees, and respirations increased slightly. The animal appeared well four days later when it was chloroformed. The transverse colon and cecum were found to be extremely hyperemic; the

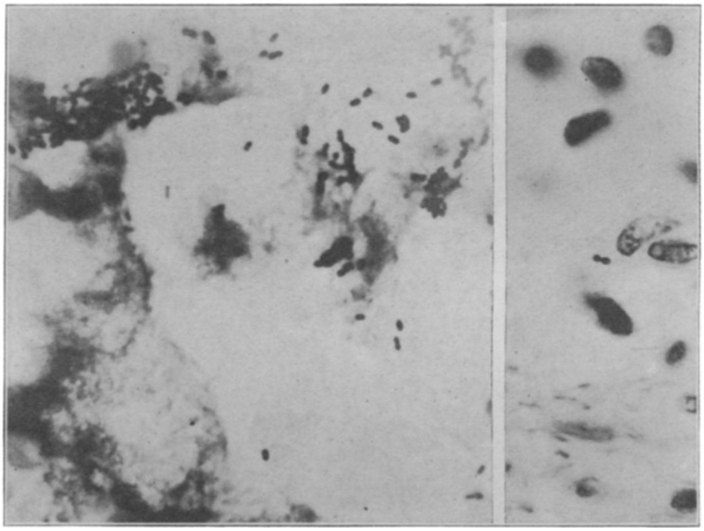

Fig. 3.—Diplococci in ulcerating area shown in figure 2 at a and b.

intestinal contents contained an abnormal amount of mucus, but otherwise showed no lesions; there was a large subcapsular hemorrhage in the lower pole of the left kidney, consolidation of the upper one-third of the right diaphragmatic lobe, and marked congestion and mucopurulent material in the mucous membrane of the trachea and nose. Cultures from the blood and the uterus were negative; the mucous membrane of the nose and trachea contained a large number of green-producing streptococci and staphylococci. In the guinea-pig injected with the pure culture of the green-producing streptococcus a diminution of 33 per cent. in leukocyte count and a slight increase in respiration occurred the day following the injection. Two days after the injection, when the animal appeared quite well, it was chloroformed. Examination revealed uniform grayish areas of consolidation of the right diaphragmatic lobe, a few hemorrhages in the mucous membrane of the stomach along the lesser curvature and cardiac end, but no lesions of the intestine. The cultures from the lung contained a moderate number of colonies of staphylococci and green-producing streptococci.

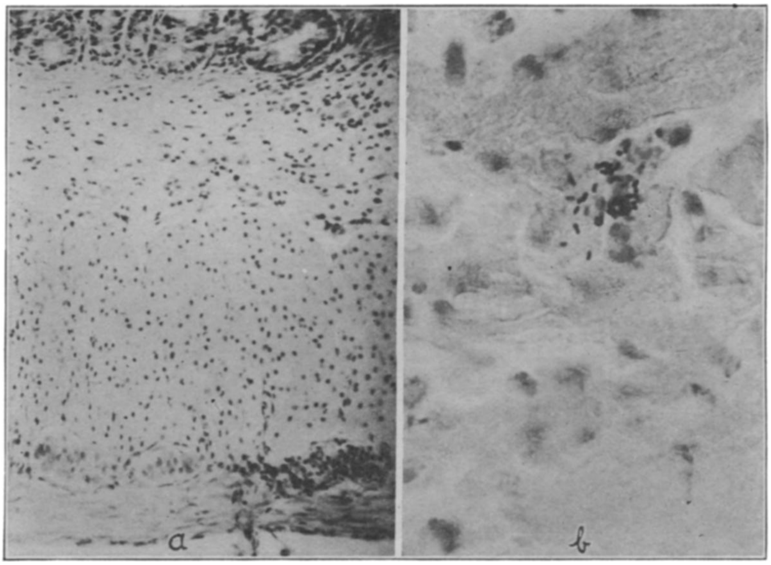

Fig. 4.—Section of the ileum of a guinea-pig injected intrarectally with a suspension of hemorrhagic mucus from the stool in case 2981. Hemorrhage and infiltration and thrombosis of vessel in subperitoneum by leukocytes and by swollen degenerating, desquamated endothelium; gram-positive diplococci in the area of infiltration in the submucosa. a., Hematoxylin and eosin, × 100; b. Gram-Weigert, × 1000.

Many green-producing streptococci were isolated from the lesions in the intestines of the patient with the fatal gastro-intestinal infection (case 2979), and from stools in the sister of this patient whose attack was milder and who recovered (case 2981). These attacks occurred at a time when influenza was epidemic in the surrounding community. The organism was present in large numbers in the lesions of the intestines and stomach, and absent in the normal tissues. Injection of the freshly isolated strains from these 2 patients into 14 animals produced well marked lesions in the gastro-intestinal tract, in 12 in which the organism was demonstrable in large number; the lesions were similar to those noted in the patients. In view of these facts there can be no reasonable doubt that this organism was the cause of the gastro-enteritis in these patients. Lesions of the gastro-intestinal tract following injection of streptococci isolated in influenza were noted only occasionally, but they occurred more often after one or more animal passages. Thus from a series of 176 animals (guinea-pigs, rats, and dogs) injected in various ways with strains from influenza, outspoken hemorrhages of the stomach were noted in 9, hemorrhages or other lesions of the intestines in 12, and hemorrhagic pancreatitis in 5. Cholecystitis did not occur in a single case. The hemorrhages followed injection of the strains as isolated from influenza in 6 instances; the others occurred in animals injected with strains after from one to four animal passages. The lesions of the

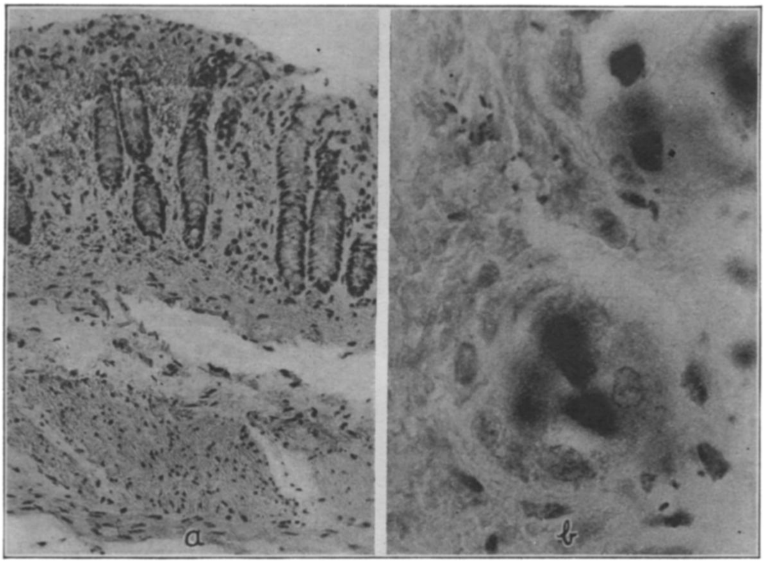

Fig. 5.—Section of transverse colon of a rabbit injected intragastrically with a strain in the fourth animal passage; marked infiltration by red blood corpuscles throughout the mucosa; gram-positive diplococci in the interstitial tissue between the acini. a, Hematoxyln and eosin × 100; b, Gram-Weigert, × 1000.

stomach consisted usually of multiple punctate hemorrhages varying in size, but whether small or large they usually involved considerable areas (fig. 4). Marked edema, and at times necrosis with beginning ulceration of tissue was often associated with the hemorrhages. Postmortem digestion was often marked. Sections and cultures made in some instances showed that the lesions were the result of localization of streptococci and not due wholly to general toxic effects. Moreover, in nearly all instances the hemorrhage in the stomach occurred only when the virulence was high and when streptococci were isolated from the blood after death. Besides the swelling, hemorrhage, and the edema of Peyer's patches, lymphoid follicles, and mesenteric lymph glands, the most common lesions of the intestinal tract consisted of small but usually numerous hemorrhages of the mucous membrane or submucosa. The hemorrhages were more common in the small intestine but occurred also in the cecum, transverse colon (fig. 4 b), and in one instance in the appendix of a rabbit. The mucous membrane in the area showing hemorrhages was usually covered with a blood tinged mucus. Large amounts of mucus and fluid contents in the intestine were noted in some instances in which the mucous membrane was hyperemic. Peyer's patches and the lymphoid follicles were swollen, but no hemorrhages could be made out. Only a few animals developed outspoken diarrhea. Sections of the intestines through the hemorrhagic areas showed most of the hemorrhages to be in the mucous membrane. The areas were often wedge shaped, with the base toward the lumen, but they extended well into the deeper layers and mucosa, and in some instances into the submucosa. Superficial erosions were noted in some instances, but marked ulcerations were not found. In either case gram-positive diplococci were easily demonstrable throughout the areas, but not in the normal tissues. The diplococci were most numerous near the surface of the hemorrhage, as if the bacteria had been excreted into the lumen of the intestine, but at times they were found in large numbers in the deeper layers of the mucosa. Leukocytic infiltration was quite marked in some instances, and wholly lacking in others. Marked damage to the endothelium of the blood vessels was noted in many sections in, or adjacent to, the areas of hemorrhage and infiltration. In some cases this was evidenced by swelling of the endothelium and irregular staining of the nuclei; in others by the occurrence of masses of desquamated, swollen endothelial cells, with fragmented nuclei, partly or completely plugging the lumina of fair sized vessels. This finding was similar to that of Kuskow in lesions in the intestines in influenza in man. The lesions were particularly common in the vessels in the subperitoneum. More rarely the vessels were filled with leukocytes in which only a few endothelial cells could be found (fig. 4 a). Cultures from the upper intestinal contents, rich in mucus, and of emulsions of washed pieces of hemorrhages from the mucous membrane often yielded a large number of the green-producing streptococci, cultures from the lower respiratory tract usually only colon bacilli. Localization in the intestinal tract rarely occurred following the injection of the hemolytic streptococcus isolated in influenza, but in two instances in which hemorrhages were found, hemolytic streptococci were isolated in large numbers and diplococci were demonstrated in the lesions.

If lesions developed in the pancreas, they were usually severe, and always most marked in the head. They consisted of marked edema, diffuse and circumscribed hemorrhages usually associated with fat necrosis (fig. 4). Sections showed marked separation and degeneration of parenchymatous cells, edema, hemorrhage, and moderate infiltration of interstitial tissue. Some of the capillaries and larger vessels were partially or completely plugged with desquamated and degenerating endothelial cells. Gram stains revealed many diplococci in the thrombosed vessels and throughout the hemorrhagic and edematous areas, but the organisms were not demonstrable in the lumina of vessels and in the tissues, which were unchanged.

The islands of Langerhans were changed little or not at all, and were quite free from bacteria. The lesions noted following the injection after animal passages of strains from cases in which there was no gastro-enteritis, were due to localization of streptococci and not wholly to general toxic effects. They were similar to those noted following injection of the two strains from the cases of gastro-intestinal influenza, similar to those found in persons during the pandemic of 1889 to 1890, and the pandemic of 1918-1919 (Kuskow, Lucke, Wight and Kime). They occurred following intravenous, intraperitoneal, and intratracheal injection, and after introduction into the stomach, duodenum, and lower bowel.

Localization in the gastro-intestinal tract was found to be due largely to peculiar qualities in the streptococci. It occurred in nearly all animals injected with strains from the patients who had similar lesions. It occurred even in different species after injection of some strains isolated from cases of respiratory influenza after one or more animal passages. Thus a strain that produced pancreatitis in a guinea-pig in the second passage produced this condition in the guinea-pig, rat and dog on intravenous injection in the third passage, a property which had disappeared in the fourth passage. The strain from case 2979 was agglutinated specifically by the monovalent antistreptococcus serum from influenza.

The experiments made as a basis of this study suggest that there is a true gastro-intestinal type of influenza and that green-producing streptococci similar to those isolated from the respiratory type of the disease but which tend to localize in the gastro-intestinal tract, are the chief cause. It is not to be concluded, however, that all symptoms in influenza referable to the gastro-intestinal tract are due to localization of bacteria in its mucous membrane. In experiments reported elsewhere[3] it has been shown that the symptoms and findings in influenza are due in part to an anaphylactoid reaction; the severe vomiting and diarrhea noted at the outset of some cases may be an expression of this mechanism.

BIBLIOGRAPHY

[1] Kuskow, N.: Zur pathologischen Anatomie der Grippe, Virchows Arch. f. path. Anat. u. Physiol., 1895, cxxxix, 406-458.

[2] Lucke, B., Wight, T., and Kime, E.: Pathologic Anatomy and Bacteriology of Influenza, Epidemic of Autumn, 1918, Arch. Int. Med., 1919, xxiv, 154-237.

[3] Rosenow, E. C.: Studies in Influenza and Pneumonia. VII. A Study of the Effects Following the Injection of Bacteria Found in Influenza in Normal Throats, in Simple Naso-Pharyngitis, and in Lobar Pneumonia. (This issue, p. 504.)

[4] Sherwood, N. P., Downs, C. M. and McNaught, J. B.: Nonlactose Fermenting Organisms from the Feces of Influenza Patients, Jour. Infect. Dis., 1920, xxvi, 16-22.